Clinical malaria diagnosis in adults: the value of signs, symptoms and antibodies

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ABSTRACT

In the absence of microscopic examination, the high prevalence of asymptomatic malaria infections and the non-specific symptoms of the disease make clinical diagnosis difficult in highly endemic areas. Data from daily medical records of 111 adult volunteers obtained in a 13-month longitudinal survey were analysed using Pearson's correlation to investigate the relationship between parasitaemia and clinical symptoms and to determine the predictive strength of various clinical symptoms for malaria. Forty three per cent of the subjects were blood smear positive at one or more times in the study. Parasite prevalence and clinical symptoms followed a seasonal distribution, being higher and occurring more often in the high transmission periods. High antibody responders to the circumsporozoite protein (CSP) showed lower parasite prevalence and fewer symptoms compared to the other responders. Malaria parasitaemia was significantly correlated with fever ($p < 0.01$). Fever, joint pain and headaches could be useful in endemic areas as symptom indicators of malaria for adults.

INTRODUCTION

Malaria, particularly that caused by *Plasmodium falciparum*, remains one of the most serious diseases in the world, endangering infant and early childhood development in many tropical regions that lack the resources to implement thorough widespread control programmes.[1] The disease threatens about 2.2 billion people, about 40% of the world's population.[2] In tropical Africa where the disease is deeply entrenched, no fewer than 373 million people live in endemic areas,[3] where the dominant parasite is *Plasmodium falciparum* and where the number of clinical cases has been estimated at between 76 and 150 million annually.[4,5] Mortality due to malaria is placed at between 1.5 and 2.7 million deaths each year.[6] About 90% of all malaria cases are in sub-Saharan Africa, two-thirds of the remaining cases are concentrated in Brazil, India, Vietnam, Cambodia, Sri Lanka, Afghanistan and Solomon Islands. With the emergence of insecticide-resistant anopheles mosquitoes and drug-resistant *P. falciparum*[7], the global prospect of malaria eradication has remained unaccomplished.

In most endemic countries, the goal of malaria control is to prevent malaria mortality and to reduce morbidity and the socio-economic losses occasioned by this disease. Success in achieving these noble goals will depend on strong political commitment and a change of orientation from a highly prescriptive centralised control programme to flexible, cost-effective and sustainable programmes adapted to local conditions. It will also depend on responding to local capacities for assessing malaria situations and selecting appropriate control measures to reduce or prevent the disease problem.[2] Five basic technical elements of this control strategy include (1) the provision of early diagnosis and treatment of malaria; (2) planning and implementation of selective and sustainable preventive measures including vector control; (3) detection of early epidemics with a view to containing or preventing them; (4) strengthening of local capacity in basic and applied research to promote the regular assessment of a country's malaria situation, in particular the ecological, social and economic determinants of the disease; and (5) research geared towards the synthesis of alternative therapeutic treatment and possible vaccine development.[8]

The biology of *P. falciparum* as well as its life cycle has led to the identification of two major extra-erythrocytic developmental stages of the parasite as targets for antibody attack. These are the sporozoite and merozoite stages whose antigens are currently being evaluated for inclusion in a malaria vaccine.[9] The protective value of anti-sporozoite (anti-CSP) antibodies remains a matter of debate but these antibodies, which increase with age and cumulative sporozoite exposure,[10] have become an important indicator of transmission intensity or risk of exposure to malaria infection and, thus, an important epidemiological tool.

Early and correct diagnosis of malaria, a key issue in the control of mortality and morbidity, is today conducted in the language of molecular biology and immunology.[5,11] However, the vast majority of deaths occur among young children in Africa especially in rural areas in the absence of microscopic examination and proper health care services.[6] Some studies[12-14] have shown that only a small proportion of those treated for malaria actually had positive parasitaemia upon blood smear examination.

The aim of the present study is to determine whether clinical diagnosis of malaria can be improved with an algorithm developed using antibody levels to the circumsporozoite protein (CSP), symptoms and parasitaemia. Other workers have investigated the correlation between parasitaemia and the entomological inoculation rate and between sporozoite exposure and ELISA absorbance values. This work will attempt to investigate the correlation between clinical symptoms and parasitaemia.

MATERIALS AND METHODS
Study area

Igbo Ora is a rural community located 100km west of Ibadan. There is a community health care programme run by the College of Medicine, University of Ibadan, with the collaboration of the local government council and the government of Oyo State, thus making Igbo Ora an attractive site for field studies. Villages in the Igbo Ora and Idere areas of Ifelolu Local Government Area of Oyo State were selected as study sites based on their proximity to Igbo Ora. These villages include Sekere, Geke, Iseme, Babaleshin, Araromi, Tobalogbo and Aferu. The people are mainly farmers and the area experiences a rainy season between April and October and a dry season from November to March.

Study design

The study spanned a period of 13 months (April 1992 to May 1993). Volunteers were recruited at different periods of the low transmission season (April 7, 21, May 5 and June 2, 1992). A system of home visits was used where the subjects were seen daily in their homes or in their farms (except on Saturdays and Sundays). Each home visitor took care of the general welfare of 10–15 subjects, monitoring their malaria status, health and intake of herbal antimalarial infusions (*agbo*). Daily medical records were kept on each subject in the daily malaria record booklet with the aid of a questionnaire. Blood samples (500µl) for parasitological and serological investigations were also collected from each subject fortnightly.[1]

Subjects

An initial 183 subjects were enrolled for the study, but only 111 participated till the end of the study period in April 1993. All the volunteers were adults (male and female) between 25 and 50 years. Pregnant women were excluded from the study for cultural reasons.

Data collection

The parasitaemia data and the enzyme linked immunosrbent assay (ELISA) values of antibodies to the *P. falciparum* circumsporozoite protein available for each subject[1,15] were used for this study. The symptoms reported by the subjects were extracted from the questionnaire, collapsed and entered as one reading on two-week intervals to correspond with the parasitaemia and ELISA results. All the entries were done with the *Microsoft Excel 2000* statistical package.

Statistical analysis

The 111 subjects were grouped on the basis of their parasitological and serological results and on the symptoms reported.[1] Forty eight subjects (43%) were confirmed to be infected with malaria, with positive blood smear at one or more times in the study period. Forty subjects (36%) were neither parasitaemic nor symptomatic while 23 subjects (21%) were suspected to be infected with malaria, having showed symptoms, although no parasite was found in their blood smears. Similarly, four groups were recognised based on their mean absorbance (ELISA) value throughout the study[1] — non-responders (6.3%), with a mean absorbance of less than 0.11; low responders (31%), with a mean absorbance of 0.11–0.20; moderate responders (55%), with mean absorbance 0.21–0.49; and high responders (8%), with mean absorbance greater than 0.50. This information was combined to produce 12 categories of subjects.

Group 1	—	Malaria confirmed, high responders
Group 2	—	Malaria confirmed, moderate responders
Group 3	—	Malaria confirmed, low responders
Group 4	—	Malaria confirmed, non responders
Group 5	—	Asymptomatic, non-parasitaemic, high responders
Group 6	—	Asymptomatic, non-parasitaemic, moderate responders
Group 7	—	Asymptomatic, non-parasitaemic, low responders
Group 8	—	Asymptomatic, non-parasitaemic, non-responders
Group 9	—	Malaria suspected, high responders

Group 10 — Malaria suspected, moderate responders

Group 11 — Malaria suspected, low responders

Group 12 — Malaria suspected, non-responders

For each of these categories, correlation values were calculated for ELISA absorbance, parasitaemia and symptoms. Analysis was done using the *Microsoft Excel 2000* and *SPSS 7.0* statistical packages.

RESULTS

The present study sought to determine the predictive value of clinical malaria symptoms in a confident diagnosis for malaria in a rural adult population of Nigerians whose antibody response to the circumsporozoite protein (CSP) of *Plasmodium falciparum* had previously been studied.[1,15]

Of the clinical symptoms being investigated, the commonest was joint pains (75.9%), followed by headaches (15.7%) and fever (8.4%) (Table 1). These symptoms followed a seasonal distribution, with a higher occurrence in the rainy season (89.7%) than in the dry season (10.3%). Results show 9.4% observed parasitaemia occurring during the dry months (weeks 40–54) with the majority clustered within the rainy season (Table 1).

Table 1 Prevalence of malaria parasite and clinical symptoms in the volunteers, observed every two weeks in 1992/93

Week	Fever	Phead	Pjoint	MP
0	0	0	1	0
2	3	1	4	0
4	0	2	4	0
6	0	0	2	0
8	1	0	2	0
10	1	1	5	1
12	1	1	8	0
14	0	1	3	3
16	0	0	15	4
18	0	2	15	5
20	0	1	7	1
22	0	3	6	1
24	0	1	1	2
26	0	0	4	1
28	0	1	7	2
30	1	0	3	4
32	1	2	5	4
36	4	5	14	1
38	0	0	6	0
40	0	1	2	0
42	0	2	3	0
44	0	1	4	0
46	0	0	0	0
48	0	1	1	0
50	0	0	0	1
52	0	0	0	2
	14 (8.4%)	26 (15.7%)	126 (75.9%)	32

Phead = headaches; Pjoint = joint pains; MP = Malaria parasite

Parasitaemia was recorded in week 22 among those confirmed to be infected with malaria, high responders. Joint pains had the highest frequency among this group of subjects and were reported on weeks 10, 18 and 28. In this group, headaches were recorded only in week 40. No fever was recorded among these subjects. A very weak negative correlation between parasitaemia and headaches (r = -0.038), and between malaria parasite and pain in the joints (r = -0.069) was observed.

Mean ELISA absorbance for those confirmed to be infected with malaria, moderate responders (group 2) peaked at week 22 and 24. Subjects in this group reported more symptoms than other malaria confirmed subjects; joint pains were the most frequent. Positive blood smears clustered within the rainy season with two positive cases recorded during the dry months. Fever was seen in week 30. There was a moderate correlation between parasitaemia and fever (r = 0.346), parasitaemia and pain in the joint (r = 0.352), and parasitaemia and absorbance value (r = 0.305).

The ELISA absorbance profile of the malaria confirmed low responders fluctuated most in week 26 (Figure 1). There was no parasitaemia detected outside the rainy season and few of the symptoms observed occurred during the dry months (Figure 1). Joint pains occurred most frequently in this group, followed by headaches and then fever. There was a significantly high correlation between parasitaemia and fever (r = 0.679, p = 0.0001). There was a relatively weak correlation between parasitaemia and headaches (r = 0.341) and with joint pain (r = 0.30); fever was correlated with headaches (r = 0.365). Thus, there was a significant correlation between parasitaemia and fever especially among the low antibody responders to CSP.
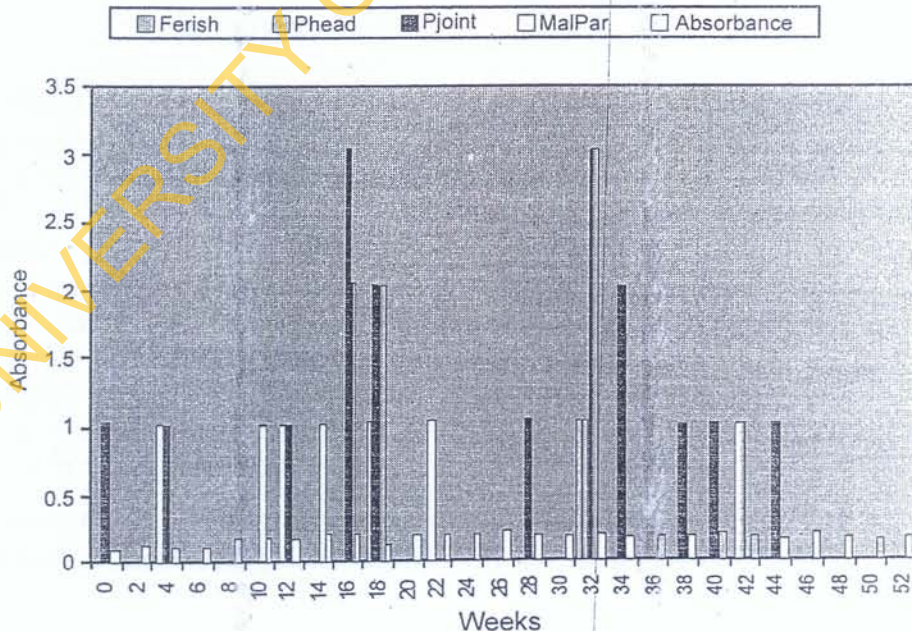

Figure 1 **Prevalence of Malaria Symptoms and anti-CSP antibodies absorbance in subjects who were malaria confirmed and low-responders**
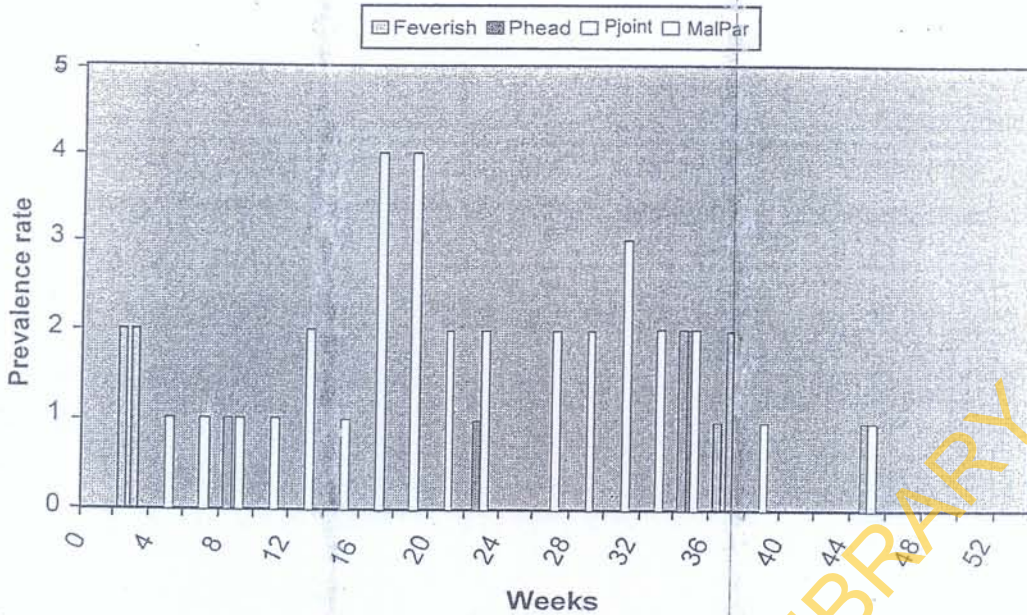
Figure 2 Prevalence of Malaria Symptoms in subjects who were non-parasitaemic and asymptomatic

Among subjects confirmed to be infected with malaria who were non-responders to the CSP, parasitaemia was recorded throughout the transmission season. Peak ELISA absorbance was observed in week 20. In this group there was a very weak correlation ($r = 0.11$) between parasitaemia and joint pains, and absorbance values had a significant correlation with both pain in the joint ($p = 0.022$) and headaches ($p = 0.034$). As expected, subjects confirmed to be infested with malaria manifested more (42.2%) of the symptoms observed than the non-parasitaemic, asymptomatic (immune) subjects (Table 2).

Among immune subjects, joint pains had the highest occurrence (Figure 2). Symptoms occurred more often during the rainy season with only a little proportion recorded outside this period. No malaria parasite was observed in the blood smear of the immune subjects throughout the entire study period. High responders showed very few symptoms of malaria; they had only joint pains. There was a negative correlation between antibodies to CSP and pain in the joint ($r = -0.238$). Among this group of non-parasitaemic and asymptomatic subjects, no significant correlation between any of the symptoms was recorded.

All subjects suspected to have malaria manifested symptoms but were not parasitaemic throughout the study period (Figure 3). Among the high antibody responders fever and headaches were recorded in week 10 while joint pains were observed in weeks 10, 22 and 34 (Figure 3). There was a high correlation between fever and joint pain ($r = 0.555$; $p = 0.002$). Similarly, a positive significant correlation was observed between fever and joint pains among the other categories of responders ($p = 0.014$). There was also significant correlation between antibodies to the CSP and joint pains ($p = 0.04$).

Table 2 Prevalence of clinical symptoms recorded by malaria confirmed, malaria suspected and non-parasitaemic asymptomatic subjects

Categories of subjects	Fever	Phead	Pjoint	Total
Malaria confirmed	2	15	53	70 (42.2%)
Non-parasitaemic	6	4	46	46 (27.7%)
Asymptomatic	6	7	37	50 (30.1%)

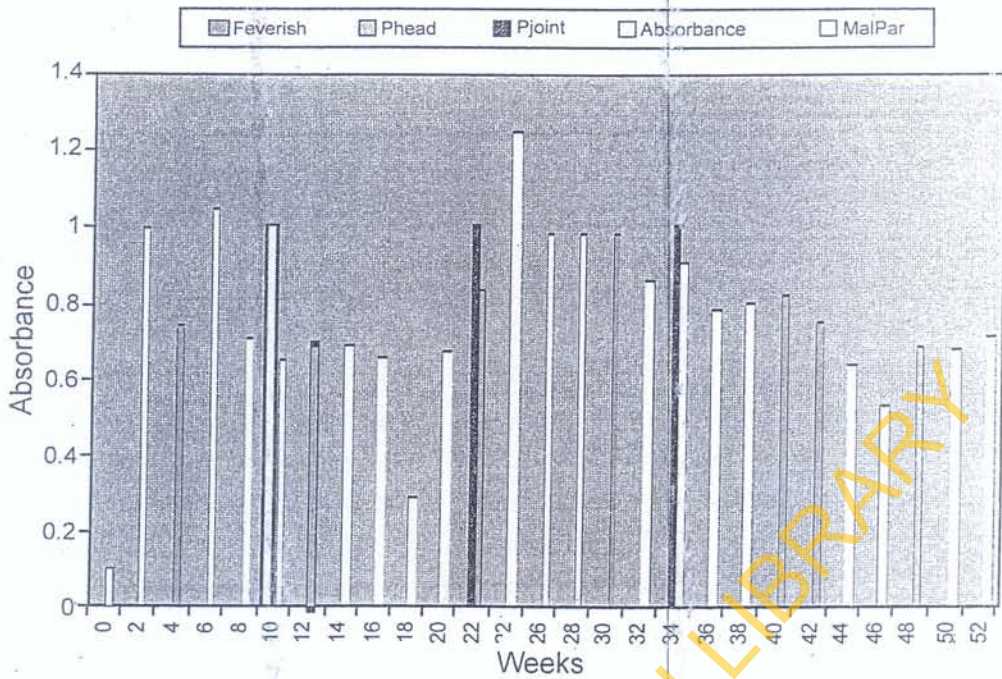*Phead = headaches; Pjoint = joint pains*

Figure 3 Prevalence of Malaria Symptoms and antibodies absorbance in subjects who were

Malaria suspected and high-responders

DISCUSSION

The main aim of this study was to assess the relationship between clinical malaria symptoms and blood stage parasites with a view to defining specific clinical algorithms for diagnosis in adults.

The World Health Organization[6] recommended that in places without properly equipped health centres, primary health workers, on the basis of clinical diagnosis, should administer treatment for malaria. Several studies have evaluated the accuracy of this diagnostic method as compared to the gold standard microscopic blood smear examination. Some found that clinical diagnosis had a poor accuracy and a low predictive value[11,16-18]; others thought that the diagnostic value of clinical symptoms could be improved by using more specific clinical algorithms.[19-22]

The seasonality in the prevalence of malaria parasites as observed in this study (Table 1) is consistent with other literature in this area, where majority of the positive blood smear observations clustered within the rainy season. Nwagwu et al observed that persons living in high malaria endemic areas appear to clear parasites during periods of reduced transmission associated with the dry season and become re-infected after the beginning of the following rainy season. A study with Liberian adults[23] showed that even highly immune adults experience higher parasite loads in seasons with increased transmission, but in a later work[24] malaria prevalence increased in the rainy season and decreased with age. Since malaria parasites are more likely to cause a patient's illness when they are present at high rather than low density,[17] an appreciation of the seasonal fluctuations in the endemicity of an area, together with the age-dependent trend of parasitaemia could help define the threshold of parasitaemia (critical level) required for individual diagnosis.[21,22] This will enable a separation to be made between clinical cases of malaria (malaria attacks) and asymptomatic infections (asymptomatic parasitaemia) in a specific

community.[21,22,25] Parasite prevalence was generally low among the adult volunteers examined, which is in line with the expected over-dispersion of parasite burdens within the younger children.[26] However, in an area of high stable transmission rates, most or all of the population is parasitaemic at any time.[10] This apparent contradiction was however explained[27] thus: although about half the children in such high endemic areas had malaria parasites at any given time, two thirds of the microscopically negative individuals were found to have harboured sub-patent levels of *Plasmodium falciparum*, suggesting that more than 90% of the exposed population at any time, i.e., in a cross-sectional survey, are chronically infected. Thus, the range of parasite loads harboured by humans with various degrees of exposure is remarkably large and probably reflects a large range of effectiveness of the defence mechanisms against malaria parasites, none of which is fully efficient.

The duration of symptoms in this study was short, usually being cleared within a week (Figures 1-3). This is in contrast to the significantly longer duration of fever, symptoms and parasite clearance among younger children. This suggests that of the two components of protective immunity, anti-parasite immunity and anti-toxic immunity, only the first plays a major role as age increases.[28]

The high responders in the malaria confirmed group also recorded the least parasitaemia (Figure 2). In a study[29] among children aged 1–11 years in the Gambia, it was observed that children who entered the malaria season with significant levels of anti-CSP antibodies experienced fewer clinical attacks, although such seropositive children formed a small minority of the study cohort. Other workers[30,31] support the view that adults with higher levels of anti-CSP antibodies are less frequently parasitized than those with

lower antibody levels and should record less clinical attacks. This is particularly true in the dry season when the sporozoite inoculation rates are very low.

A significant correlation was observed between malaria parasitaemia and fever especially among subjects confirmed to have malaria and who had low levels of antibodies to the CSP. These results agree with a study in Papua, New Guinea,[32] where a history of fever with no other major symptom (i.e., cough, diarrhoea or constipation) was the best predictor of a positive blood slide in the adults examined. High fever of short duration in Mali was more likely to be associated with malaria than with other illnesses.[19] Similarly, report from Tanzania[5] shows that a history of intermittent fever was strongly associated with a diagnosis of malaria. Furthermore, from results of clinical studies in Dielmo, Senegal, an area holoendemic for malaria,[17] malaria attack was defined as clinical episodes with fever (body temperature greater than or equal to 38.0°C) or reporting fever, headache or vomiting, associated with a parasite: leukocyte ratio above an age-dependent pyrogenic threshold identified in that community.

Although research report from adult Liberians[23] concluded that under conditions of intense perennial transmission and in subjects over 15 years of age, neither histories of fever, headaches, joint or body pains nor body temperature measurements are suitable guides to malaria morbidity. Findings from the present study suggest the contrary and perhaps further underscore why clinical guidelines based upon parasitaemia and symptomatology must be adjusted according to the intensity of transmission and should be specific for each geographical area.[22] No significant correlation between joint pains, headaches and fever was recorded among the non-parasitaemic asymptomatic group. Their high antibody levels may account in part for this. Thus, the presence of these symptoms

in the subjects could be attributable to any other tropical fevers or to other factors such as the occupational hazards of the community.

Clinical diagnosis of malaria is complicated by the prevalence of asymptomatic infections and non-specific signs and symptoms of the disease, which could lead to over-diagnosis and over-dispensing of drugs. This study however corroborates findings[26] that the subjective symptoms (headache, joint pain, tiredness) are more important indicators of parasitaemia in the adult group than the classical paediatric signs (vomiting and diarrhoea) in younger children. In agreement with the current practice of clinical diagnosis of malaria as recommended by the WHO[20], in the absence of microscopical examination of blood smears in endemic areas and at the risk of leaving clinical attacks of malaria untreated, or what is worse, progression to severe malaria, clinical diagnosis based on the presence of fever, joint pains and/or headache could be useful and practical unless symptoms or signs highly suggestive of another illness that could cause fever are present.

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